LESIONS FOLLOWING THE USE OF ERTRON IN RHEUMATOID ARTHRITIS *

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The literature is replete with reports of the administration of various preparations of vitamin D, principally in the therapy of rickets and rheumatoid arthritis. Toxic symptoms in the form of anorexia, nausea, headache, polydypsia, and polyuria are known to occur with varying doses. That anatomic lesions must occur is manifest by the urinary changes and by tests showing impaired renal function and chemical alterations in the blood.[1-5] Only five patients whose deaths have been ascribed to large doses of vitamin D have been autopsied and all were infants.[6-9] Because lesions observed at necropsy following the prolonged use of Ertron † have not been described previously, the following case report is of interest.

REPORT OF CASE

E. P., a white female artist, 63 years old, was admitted to Goldwater Memorial Hospital for the first time in December, 1942. She stated that she had had pains and progressive deformity of the joints of the extremities for 18 years. Until 2½ years before admission she had received no medical treatment. At that time she was given approximately 100 intramuscular injections of gold extending over a period of 1 year. Her condition improved, but had relapsed after 4 months. Otherwise her past history included nothing relevant to her present condition. Physical examination revealed marked deformity and limitation of motion of the joints of the extremities. There was scoliosis of the lower spine with convexity to the left. The heart was not enlarged and the rhythm was regular. The blood pressure was 168/98 mm. Hg.

The patient remained in the hospital with a normal or slightly subnormal temperature for approximately 3 months, during which time she received x-ray therapy to the involved joints in unknown amount. She was discharged as slightly improved.

Her second and final admission occurred in August, 1945. Approximately 18 months prior to readmission she had begun to take three or four capsules (150,000 to 200,000 international units) of Ertron daily and had continued this dosage for 1 year without medical supervision. Six months before her second admission a lesion described as an "infection" developed on the right foot and discharged thick yellowish pus. Following this, numerous abscesses appeared over the dorsa of both feet, the left knee, and the dorsum of the right hand. Generalized pruritus was present but no rash was noted. The patient developed a chronic cough productive of brown but not bloody sputum. The weight loss was severe but indefinite in amount. No information was available concerning the patient's diet.

Physical examination on admission showed an emaciated, elderly female with

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† Ertron is an electrically activated ergosterol (Whittier process) marketed in capsules, each containing not less than 50,000 international units, by the Nutrition Research Laboratories, Chicago, Ill.

marked deformities of the joints. Several small, discrete, nontender lymph nodes were palpable in the axillae, and in the inguinal and femoral regions. There was a draining sinus posterior to the medial malleolus of the right foot and multiple, tender, cystic swellings on the dorsum of the right hand, the left knee, and the left foot. The heart was regular and no murmurs were heard. The blood pressure on admission was 125/85 mm. Hg.

Course. During the patient's stay in the hospital, one of the abscesses was incised and a portion of the wall was examined microscopically. The report was "chronic nonspecific inflammatory reaction with calcification." Culture of the material from the draining lesions yielded *Staphylococcus aureus* on two occasions. This was thought to be a contaminant, but following penicillin therapy the cultures became sterile. The temperature on three occasions rose to 100°F. but averaged

TABLE I

Laboratory Data

	1943	1945
Hemoglobin	12.8 gm.	6 gm.
Red blood cells	4,600,000	2,500,000
White blood cells	7,500	7,800
Erythrocyte sedimentation rates	72 mm. per hr., Westergren	
Fasting blood sugar	107 mg. %	100 mg. %
Blood urea nitrogen	18 mg. %	58 to 107 mg. %
Blood nonprotein nitrogen		172 mg. %
Total protein		6.6 gm. %
Serum albumin		4.9 gm. %
Serum globulin		1.6 gm. %
Calcium		13 to 14.7 mg. %
Phosphorus		6 mg. %
Alkaline phosphatase		9.6 Bodansky units
CO_2-combining power		68 vol. % falling to 35 vol. %
Urine	Alkaline; albumin, trace; glucose, negative; many white blood cells	10 days before death: alkaline; albumin, +; glucose, +; few epithelial cells; few white blood cells (later examinations not recorded)

about 99.4°F. The patient's urea nitrogen rose progressively from 58 on admission to 107. Blood pressure never rose above 125/85 mm. Hg. She became moribund and expired about 1 month after admission.

Summary of Roentgenologic Findings. The roentgenologic examinations of the chest in 1943 and 1945 revealed no calcific deposits in the pulmonary parenchyma. In 1943, the wrists, hands, and knees showed the characteristic changes of rheumatoid arthritis (Figs. 1, 4, and 5). These changes were extensive, with bone decalcification, destructive changes, contractural deformities of the hands, and ankylosis of the wrists. The left knee showed osseous destruction while the right showed cartilaginous destruction only. The vessels about the joints were not calcified and there were no calcific deposits in the soft tissues.

In 1945, the wrists, hands, and knees showed progressive changes due to arthritis. Despite these changes, the bones were denser and presented a more nearly normal appearance than in 1943. In fact, the entire skeleton was richer in calcium content. The vessels about the joints were calcified, notably the pelvic, femoral, popliteal, and tibial arteries. The deposition of calcium in the soft tissues presented striking appearances. The synovial membrane of the left knee was completely outlined, showing its extent, distribution, and lobulations. Calcium was also deposited within

the joint (Figs. 6 and 7). Considerable calcium was deposited in the soft tissues in and about the right wrist, thenar eminence, fingers of the right hand, and in the interosseous membrane of the forearm. Soft tissue swellings about the wrist and on the dorsal aspect of the hand contained calcium (Figs. 2 and 3). There was less calcium in the left hand, the deposit being limited to the proximal interphalangeal articulation of the ring finger; there was destruction and subluxation of the underlying joint.

Similar changes were observed in the elbows. The destructive changes were pronounced and there was calcium deposited in and about the joints, especially on the left side. Soft tissue lobulations about the joints were outlined by calcium salts. The ankles were free of destructive osseous changes but the metatarsophalangeal articulations were not. Large amounts of calcium were deposited in the soft tissues in and about the ankles and in the joints of the feet as well as in the Achilles tendon. A notable collection was present in and about the metatarsophalangeal articulation of the right big toe. A rather unusual collection was observed in the soft tissues of the left leg extending 13 cm. above the ankle, medial and posterior to the fibula (Figs. 8 and 9).

Comparative study of roentgenographs of the lumbosacral spine in 1943 and 1945 showed no marked changes. There were no calcific deposits in or about the shoulders.

Necropsy

Necropsy was performed 13 hours after death.

The deformities of the joints and other parts of the body were those noted on physical examination. The mouth was edentulous. Discrete but small lymph nodes were present in each axilla. Thick, chalky material was seen at the sternoclavicular joint and at several of the costochondral junctions. Fibrous adhesions were present over both apices and there was a rim of dense parenchyma beneath the apical pleura on both sides. This extended to a lesser degree around the adjacent periphery of the lungs. A few, firm, light pink areas bulged above the surface in all except the right middle lobe. The lungs were rust-colored and exuded large quantities of frothy material. The peribronchial lymph nodes were anthracotic.

The heart with the densely adherent pericardium weighed 360 gm. The surfaces were shaggy. The endocardium of the left auricle was not thickened. The mitral valve was not deformed and the chordae tendineae were delicate. The remaining valves were normal. There was a moderate amount of diffuse sclerosis of the coronary arteries but the lumina were patent. The ostia of the renal arteries were narrowed by sclerotic plaques. The pancreas was irregular, the normal parenchyma being replaced in the head and tail by ill defined, firm, yellow masses which on section exuded from their centers small amounts of thick, putty-like material. No dilatation of the ducts was noted and the remaining parenchyma was apparently normal. The kidneys were small, weighing 60 gm. each. The surfaces were smooth but there were numerous punctate red areas. The cortices were reduced and the pelves, ureters, and urinary bladder were normal.

Cultures of the fluctuant areas of the right hand, left foot, pancreas, and fluid from the knee joint were sterile.

On microscopic examination of the left auricle, the endocardium was found to be slightly thickened by edema and connective tissue. The subendocardial portion of the auricular myocardium was replaced by a series of poorly circumscribed granulomatous lesions (Fig. 10). These were made up of partially calcified, amorphous, necrotic material surrounded by hyaline connective tissue, radially arranged fibrocytes, bizarre-shaped pyknotic nuclei, and a few multinucleated giant cells. In the cytoplasm of these were particles of calcium. The myocardial fibers at the periphery of the nodules were fragmented but there was little cellular reaction about them (Fig. 11). That which was present was composed of a few lymphocytes and Anitschkow myocytes. The lesions were poorly vascularized, but in the myocardium surrounding them were several capillaries. The mitral valve showed a few vessels with intimal thickening, but was otherwise not unusual. The mitral ring contained calcium. The endocardium of the left ventricle was normal. The myocardium showed a few areas of perivascular scarring which replaced small numbers of adjacent myocardial fibers. Most of the epicardial fat of the left ventricle was replaced by a thick fibrous band of dense but well vascularized connective tissue. The surface was covered by fibrinoid exudate which was partly organized. A few polymorphonuclear leukocytes were found in the fibrous tissue.

Numerous sections through various parts of the heart showed nothing unusual. There was moderate perivascular scarring and a small amount of intimal proliferation in the small branches of the coronary arteries, but no Aschoff nodules were seen.

Sections from the peripheral portions of both lungs showed replacement of the normal architecture by fibrous tissue (Fig. 12). In some areas the alveolar septa persisted but were greatly thickened and the alveoli were reduced in size. Within the fibrous tissue were multinucleated giant cells and masses of calcium. Aggregations of necrotic polymorphonuclear leukocytes and fibrin persisted in the midst of the fibrous tissue. The bronchial epithelium in a few places contained calcium. Beneath the epithelium were spicules of calcium which had eroded the epithelium and projected into the lumen. The lumina also contained purulent exudate and coagulum. The alveolar lining, when present, consisted of a single layer of flat cells outlining the irregular dilated spaces. Some of the septa were completely calcified (Fig. 13). The vessel walls were thickened by intimal proliferation of connective tissue and calcium was deposited in a rim about the adventitia. Other

sections from the right apex showed masses of necrotic purulent exudate in hyalinized scar tissue. Fresh exudate with colonies of gram-positive cocci was noted in one area.

The thyroid contained numerous nodules composed of acini which varied in size and were surrounded by connective tissue. The small amount of calcium deposited in the scar tissue was not unusual.

One parathyroid appeared normal except for a minute cyst filled with colloid. A nodule removed as parathyroid was composed of spicules of calcium, foreign body giant cells containing particles of calcium, and fibrocytes (Fig. 14).

In the pancreas there was extensive necrosis, both of the interstitial fat and parenchyma. In abscess cavities were masses of fibrin and polymorphonuclear leukocytes. All stages of healing were seen in various sections. In large areas the parenchyma had been replaced by dense scar tissue. In these areas the ducts were dilated and filled with amorphous pink coagulum but the epithelium was normal (Fig. 16). Giemsa's and Brown's * stains failed to reveal bacteria in the areas of acute exudation. There were no calcium deposits.

Some renal glomeruli were small and shrunken, and a few were hyalinized with the capsules of Bowman thickened. The afferent arterioles and basement membranes were also slightly thickened by hyalinized connective tissue in a few areas. There was reduction of both cortex and medulla due to atrophy and disappearance of tubules, but the renal papillae were not blunted. Scattered throughout the parenchyma, but principally in the medulla, were minute foci of necrotic polymorphonuclear leukocytes, lymphocytes, and plasma cells which seemed to represent necrotic tubules filled with polymorphonuclear leukocytes, the walls of which had ruptured. In many places these small abscesses were healing. All tubules were disarranged; many were distended with various types of casts, others showed necrotic walls, and still others, hyperplasia of the epithelium. Many tubules were atrophic and filled with hyalinized and granular coagulum. A few showed calcified casts (Fig. 15). The interstitial tissue was edematous but remarkably free of infiltration except about the granulomatous lesions. The walls and pelvic epithelium were not unusual. The renal arteries showed moderate sclerosis, but calcium deposits were lacking. With von Kossa's stain large amounts of calcium which were not apparent in the hematoxylin and eosin preparations were demon-

* Brown, J. H., and Brenn, L. A method for the differential staining of gram-positive and gram-negative bacteria in tissue sections. *Bull. Johns Hopkins Hosp.*, 1931, 48, 69–73.

strated in the granular casts and in the epithelium and basement membranes of the tubules. The calcium occurred in both the convoluted and collecting tubules.

The lymph nodes revealed focal areas of necrosis similar to those found in the pancreas and kidneys. The sinusoids were filled with polymorphonuclear leukocytes.

Sections of the chalky deposits about the ribs and clavicles showed masses of amorphous material containing calcium which spread into the surrounding muscle. Many of the individual muscle fibers showed partial calcification. No osteoporosis or evidence of acute inflammation was noted.

Sections of the aorta and its major branches showed sclerotic changes of no more marked degree than might be expected in any patient of the same age.

With Brown's and Gram's stains no bacteria were found in the lymph nodes, heart, and kidneys.

Anatomical diagnoses included: Chronic rheumatoid arthritis; calcinosis involving the periarticular tissues of the extremities, the sternoclavicular joints, the costosternal articulations, the subcutaneous tissue, the myocardium of the left auricle, the lungs, and the kidneys; lobular pneumonia; acute and chronic pancreatitis with abscess formation.

Comment

The cardiac lesions observed in the left auricle are not essentially different from those described by Baggenstoss and Rosenberg [10] as occurring in rheumatoid arthritis, except that the calcification in this instance is much greater and the giant cells contain particles of calcium. Involvement of the myocardium and not of the adjacent auricular endocardium is unusual for a lesion of rheumatic origin, yet the situation in the left auricle suggests this causal factor. It is probable that this is a lesion similar to those found in the other organs. It does not resemble the degeneration and vacuolization of the myocardial fibers mentioned by Malmberg [6] as occurring following cod-liver oil therapy. The pericardial lesions had nothing to distinguish them from an organizing fibrinous pericarditis of long duration. No mention is made of the pericardium in any other cases. In this instance the pericarditis may be a manifestation of long-standing uremia, although its severity and wide distribution make this unlikely.

Despite evidence in the roentgenograms of increase in calcium in the peripheral vessels of the lower extremities, sections of the aorta and of the renal, iliac, and hypogastric arteries showed only arteriosclerosis of mild degree.

The lesions in the lung were apparently unique. It may be argued that the necrotic foci surrounded by polymorphonuclear leukocytes in the midst of the fibrous tissue are an indication of organizing pneumonia which in turn has caused the fibrous tissue proliferation. Be that as it may, we have never observed this bizarre type of calcification in other pneumonias. The location of the calcium suggests that its deposition was influenced by the rapid change in pH which occurs in the alveolar spaces.

The presence of calcium in the skin and in the periarticular tissues in conjunction with a hypercalcemia coincides with the observations of many authors.[2,3,5]

The density of all the bones was increased following the use of Ertron. This suggests that the excessive calcium was being derived from sources other than bone.

Calcium deposits have been noted grossly in the kidneys of both children and experimental animals which have received large amounts of vitamin D. Localization in and about the tubule has been recorded by many observers.[6-9,11] Calcium deposition in the kidney was not as conspicuous in the case reported here. It was demonstrated in the lumina as well as the walls of the tubules. The glomerular changes were slight. The pelves and ureters showed no evidence of previous or recent damage. The localization of the acute lesions to the tubules is interesting to note, for if this were a disseminated hematogenous lesion of a septic nature, one would expect the glomeruli to be involved. We are aware that the kidneys may have been damaged by the therapeutic use of gold, but the fact that the urea nitrogen of the blood was normal 18 months after the cessation of such therapy suggests that the damage was not severe. The lesions of the tubules were of sufficient severity to account for the mounting urea nitrogen of the blood as observed clinically.

Since impaired renal function and nitrogen retention are known to occur in connection with the toxic action of vitamin D, both in lower animals and man, and since these signs developed in this patient following the prolonged use of this substance, it seems fair to assume that vitamin D played some rôle in the clinical picture of renal insufficiency.

The pancreatic lesions were similar to those seen in the kidney, except that calcification was lacking. The persistent finding of 1 plus glucose in urinalyses may have been due to a direct effect upon the islets of Langerhans, although in the sections examined these seemed normal and numerous. No mention is made of pancreatic lesions in necropsy reports of children, or in animal experiments.[12]

The nodule removed as parathyroid was difficult to interpret. It

showed only fibrous tissue, calcium, and foreign body giant cells resembling those seen in the lungs and skin. The thyroid gland showed no such reaction, so that contiguity with this structure seemed unlikely. The other parathyroid was normal.

It is possible that this patient had a low-grade sepsis with multiple granulomatous lesions occurring in various parts of the body, the causal agent of which was obscure. However, hypercalcemia, and deposition of calcium in the periarticular tissues, alveolar septa, left auricle and kidney tubules can scarcely be attributed to sepsis. We are tempted to include the lesions of the pancreas and lymph node, and the uncalcified pulmonary lesions as additional manifestations of the same disturbance.

Summary and Conclusions

Unsupervised use of Ertron in a patient suffering from rheumatoid arthritis led to hypercalcemia, and calcium deposition in the periarticular and subcutaneous tissues, lungs, heart, and kidneys.

There were chronic and acute granulomatous lesions in the lungs, the pancreas, the kidneys, and the lymph nodes, the nature of which was obscure. It is suggested that these lesions also are related to the use of Ertron.

Extensive damage to the renal tubules formed an anatomic basis for clinical renal insufficiency.

Since this paper was submitted for publication two reports have appeared describing similar lesions observed at necropsy in adults, following extensive use of vitamin D preparations. (Bauer, J. M., and Freyberg, R. H. Vitamin D intoxication with metastatic calcification. *J. A. M. A.*, 1946, **130**, 1208–1215. Mulligan, R. M. Metastatic calcification associated with hypervitaminosis D and haliphagia. *Am. J. Path.*, 1946, **22**, 1293–1305.) The opinions expressed by these authors corroborate the statement that various acute and chronic lesions as well as calcification are related to excessive vitamin D ingestion.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 56

FIG. 1. Right wrist, 1943. Advanced rheumatoid arthritic changes. Fusion of the residuals of the carpal bones with ankylosis. Contraction deformities of fingers; destructive changes involving the metacarpophalangeal articulations of the right hand. Decalcification of bones.

FIGS. 2 and 3. Right wrist and hand, 1945. Extensive progression of the lesion. Of note is the irregular deposition of calcium in and about the bones of the right wrist and hand, in the periarticular soft tissues, the thenar eminence, the soft tissues of the fingers, and in the interosseous space. Density of the bones is greater than in Figure 1.

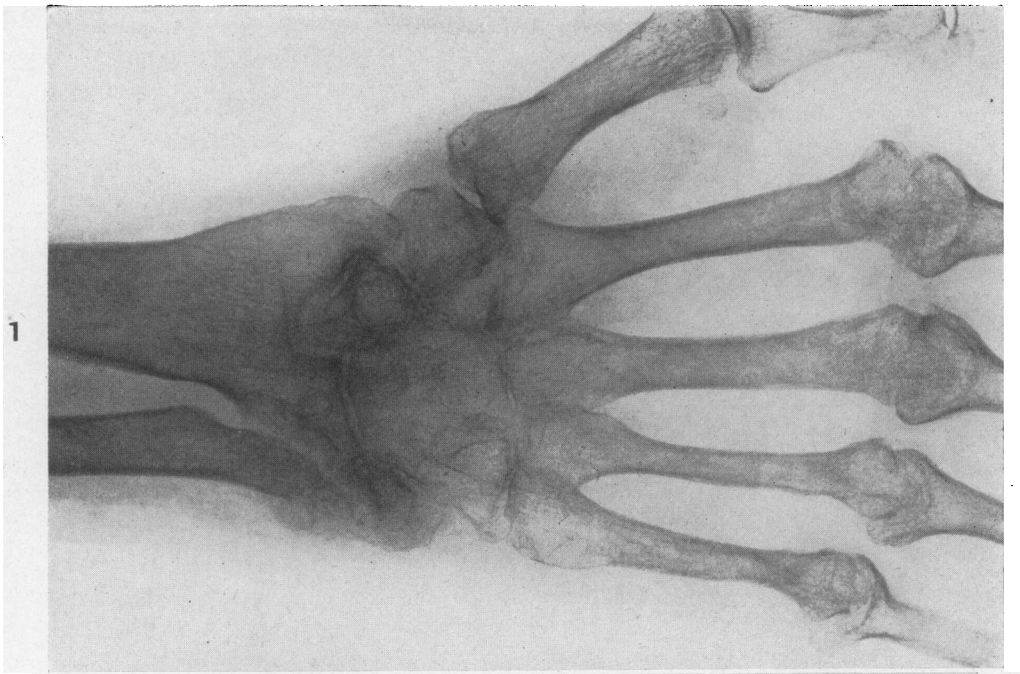
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PLATE 57

FIGS. 4 and 5. Left knee, 1943. Destruction of articulating cartilages and subchondral bone with bone sclerosis on contiguous surfaces of femoral and tibial condyles. Effusion in the joint and suprapatellar bursa. Moderate decalcification. No calcific deposits in the soft tissues. The vessels are not calcified.

FIGS. 6 and 7. Left knee, 1945. Of note are the progressive arthritic changes and increased bone density. Lateral subluxation and dense lobulated calcific deposit in the soft tissues corresponding to the synovial membrane of the knee joint. Calcific deposits in the soft tissues and in the walls of the femoral, popliteal, and tibial arteries. Increased calcification in the upper end of the tibia.


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PLATE 58

FIGS. 8 and 9. Left ankle and foot, 1945. Calcium deposited in the soft tissues in the lower third of the leg, about the tarsal bones and ankle. Large lobulated collections of calcium in the soft tissues posterior and medial to the shaft of the fibula.

FIG. 10. Left auricle showing extensive calcification of subendocardial myocardium. Von Kossa's stain. × 40.


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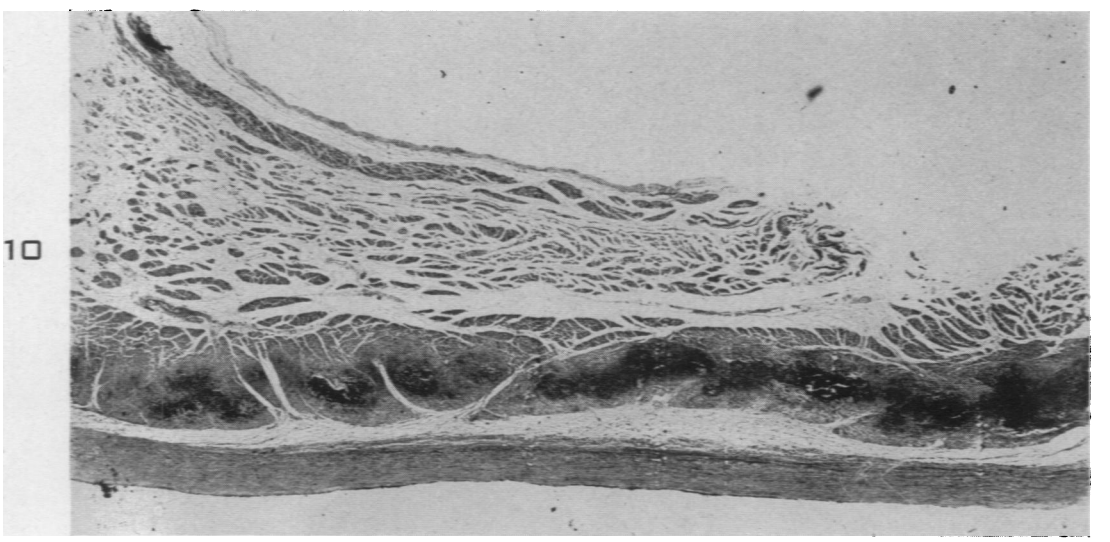
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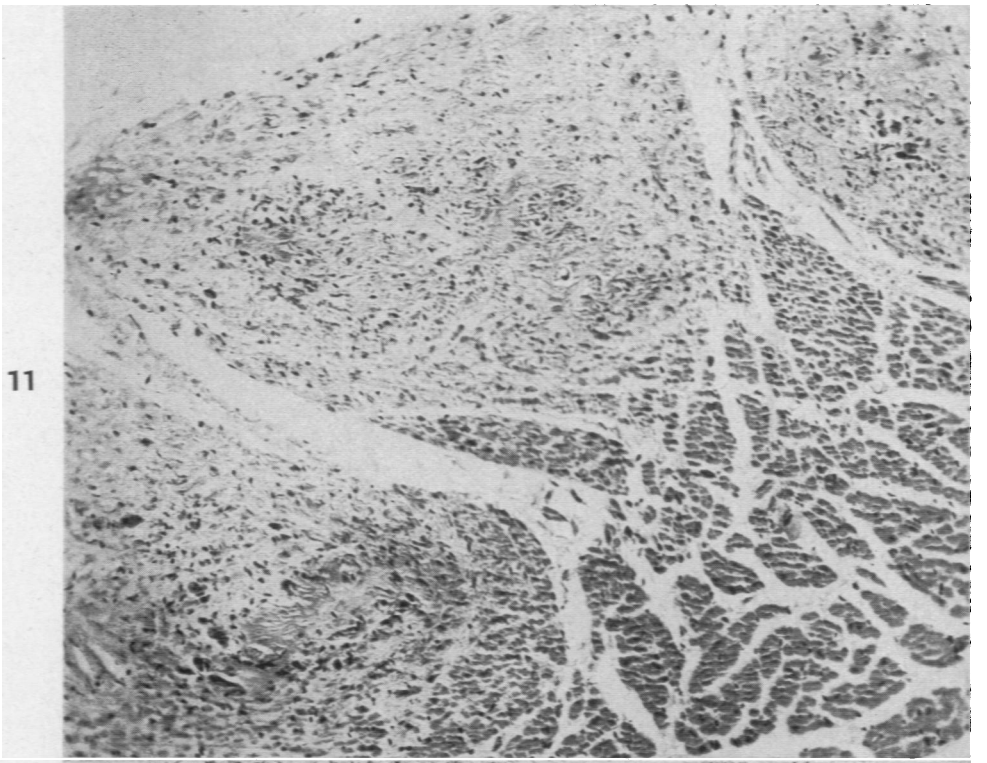
PLATE 59

FIG. 11. Higher magnification of granulomatous lesions replacing the myocardium of the auricle. Hematoxylin and eosin stain. × 165.

FIG. 12. Section of lung showing extensive fibrosis. Hematoxylin and eosin stain. × 35.



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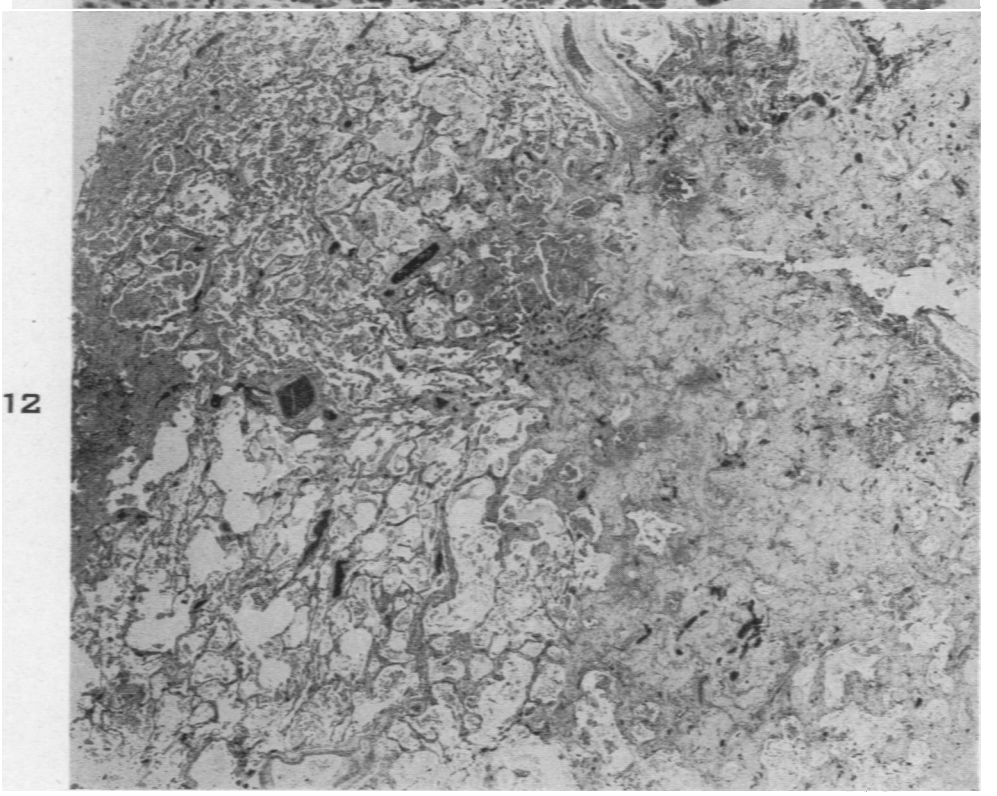

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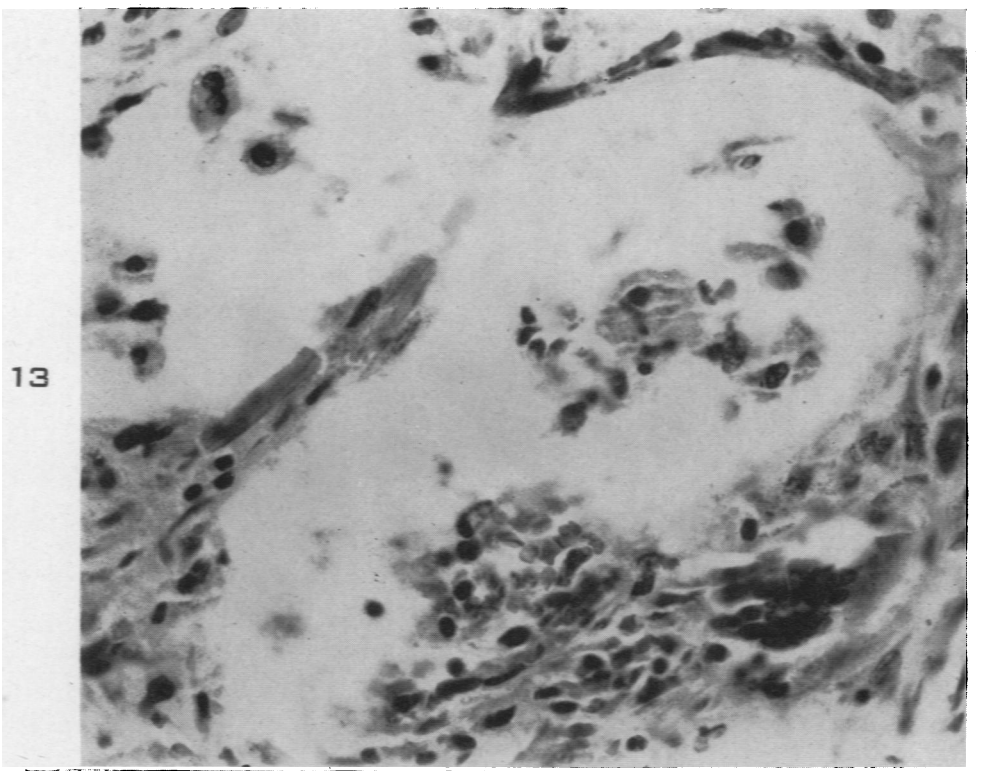
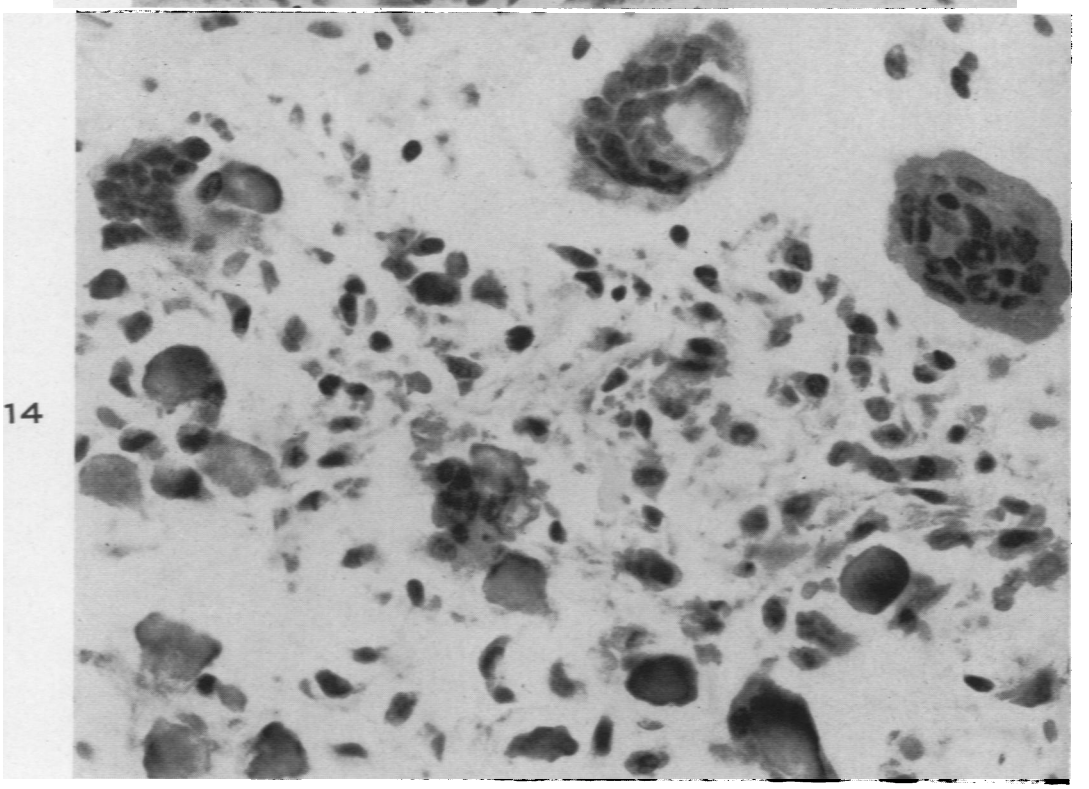
PLATE 60

FIG. 13. Higher magnification of lung. Two spicules of calcium in the alveolar septum appear to the left of the center. A foreign body giant cell is present at the lower right. Hematoxylin and eosin stain. × 515.

FIG. 14. Tissue removed as parathyroid. Granulomatous lesion typical of that seen also in the heart and lungs. Of note are the foreign body giant cells with particles of calcium within the cytoplasm and free calcium throughout the lesion. Hematoxylin and eosin stain. × 615.





Bevans and Taylor

Effects of Ertron

PLATE 61

FIG. 15. Kidney showing atrophic tubules and calcified cast at the right. Hematoxylin and eosin stain. × 125.

FIG. 16. Pancreas showing necrosis and fibrosis. Hematoxylin and eosin stain. × 40.

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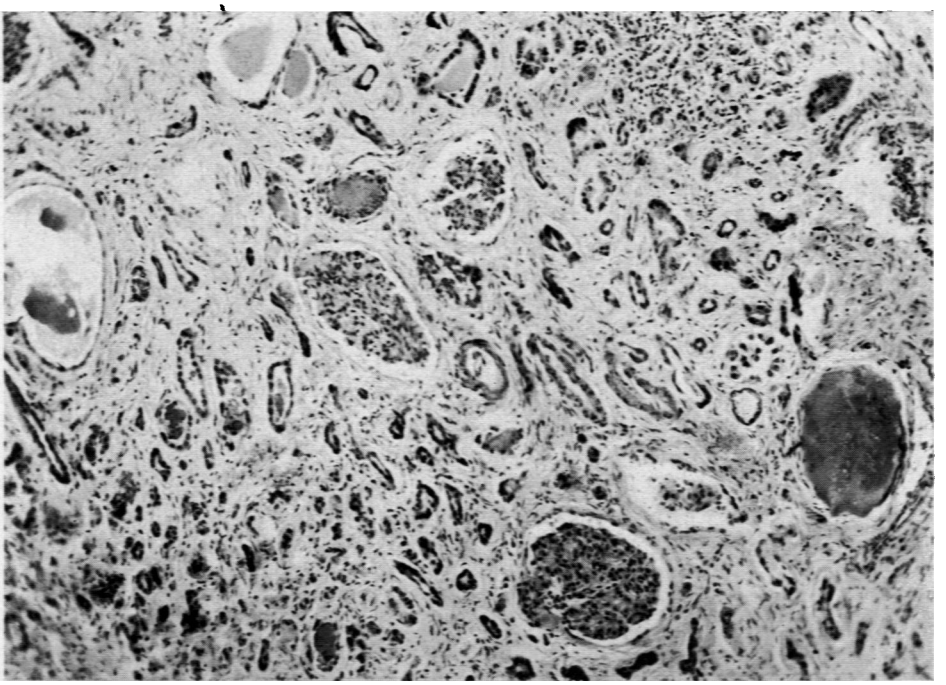

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